

# Chapter 1

## Precursor Control of Catecholamine Metabolism

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of macronutrient effects on 5-HT metabolism. The ability of nutrients to affect brain composition was first demonstrated in 1971, in experiments in which rats consuming meals containing carbohydrate and fat (i.e., lacking protein) were found soon thereafter to have increased brain levels of the essential and scarce amino acid tryptophan (Fernstrom and Wurtman 1971b). The rats also exhibited increased brain levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Fernstrom and Wurtman 1971b)—findings compatible with the view that the rise in brain tryptophan levels had increased the substrate saturation of tryptophan hydroxylase, the initial rate limiting enzyme in 5-HT synthesis (Bradford 1986). The change in levels of 5-HIAA was taken as indirect evidence that the release of 5-HT had increased in parallel (see below). The increase in brain tryptophan levels was initially thought to have resulted from the small increase in plasma tryptophan concentration that occurs in rats but not in humans after carbohydrate intake. It was unclear at that time why both plasma and brain tryptophan levels should *rise* following ingestion of a meal *different* in tryptophan, especially as insulin release (in response to carbohydrate) was known to *lower* the plasma levels of the other LNAs (Fernstrom and Wurtman 1972b). This unusual response to carbohydrate intake became understandable several years later when the binding of 5-HT to serum albumin was taken into account (Knott and Curzon 1972; Madras et al. 1974; McMenamy and Oncley 1958). Insulin, the major antihypolytic hormone, increases the transfer of free fatty acids from serum albumin to adipocytes. This transfer, in turn, diminishes the free fatty acid content of the albumin, *increasing* its affinity for tryptophan (Madras et al. 1974). Plasma levels of free (i.e., nonalbumin bound) tryptophan actually fall in response to insulin, but this decrease is compensated by the rise in albumin bound tryptophan—a moiety that is almost as accessible to brain as the “free” fraction (Yuwiler et al. 1977).

When rats were fed protein rich meals, there appeared at first to be no relationship between plasma and brain tryptophan levels; although plasma tryptophan levels rose (derived from some of the tryptophan in the meal's protein), brain tryptophan and 5-HT levels either failed to rise or, if the meal contained sufficient protein, actually fell (Fernstrom and Wurtman 1972a). It was suggested that this phenomenon reflected competition for brain uptake between tryptophan and the other LNAs that are more abundant in protein, an explanation supported by Pardridge and Oldendorff's (1986) subsequent characterization of the mechanism that transports the LNAs across the blood-brain barrier (Pardridge 1986). Tryptophan shares the LNA carrier—a facilitated diffusion system—with other LNAs

(tyrosine, phenylalanine, histidine, leucine, isoleucine, valine, threonine, methionine); the carrier's affinity for tryptophan (0.052 mM) is less than that of phenylalanine (0.032 mM) but in the same order as those of tyrosine, leucine, and methionine (Pardridge 1986). The carrier's net affinity for tryptophan, the amino acid's net flux into the brain, and, after sufficient time, even the changes in brain tryptophan levels that follow a meal, can all be estimated by calculating a “plasma tryptophan ratio”: the ratio of the plasma tryptophan concentration to the summed concentrations of the other LNAs that bind to the carrier with a reasonably high affinity (see above) (Fernstrom and Wurtman 1972a). Because all dietary proteins are considerably richer in the competing LNAs than in tryptophan, which generally constitutes only 1.0–1.5% of protein, consumption of a meal that is rich in protein (e.g., 30–40% of calories) can cause the plasma tryptophan ratio to fall, even as plasma tryptophan levels rise. Similar competitive mechanisms mediate the fluxes of tryptophan and other LNAs between the brain's extracellular space and individual neurons; however, this competition probably is not limiting, because the Vmax of transport at this locus is tenfold that at the blood-brain barrier (Pardridge 1986). Moreover, similar plasma ratios predict brain levels of tyrosine and of each of the other LNAs after treatments that modify plasma amino acid patterns (Fernstrom and Faller 1978).

At that time it was also shown that consumption of supplemental tyrosine could affect the metabolism of the catecholamines (Wurtman et al. 1974). These responses, however, were less well characterized than the effects of supplemental tryptophan on 5-HT. Evidence to date suggests that, apart from the monoamines, only a few other neurotransmitters are subject to precursor control: acetylcholine (Cohen and Wurtman 1975; Haubrich et al. 1975), histamine (Schwarz et al. 1972), and glycine (Maher and Wurtman 1980). Pharmacological doses of histidine or threonine can elevate brain concentrations of their respective neurotransmitter products, histamine (Schwarz et al. 1972) and glycine (Maher and Wurtman 1980), and choline availability is a major factor in determining how much acetylcholine is provided and released when particular cholinergic neurons fire (Maire and Wurtman 1984).

It cannot be stated for certain whether the excitatory amino acid neurotransmitters (i.e., aspartate, glutamate) are under precursor control, because the identities of the precursors for these compounds within *glutamatergic* or *aspartatergic* neurons await discovery. Similarly, experiments have not yet been done to assess the effects on GABA synthesis caused by raising brain levels of GABA's precursor,

levels of the major metabolites of dopamine (3,4-dihydroxyphenylacetic acid [DOPAC], 4-hydroxy-3-methoxyphenylacetic acid [homovanillic acid, HVA]) or norepinephrine (3-methoxy-4-hydroxyphenylglycol sulfate [MHPG SO<sub>4</sub>]) in animals given tyrosine as an index of catecholamine synthesis (when catecholamine levels remained unchanged). Interestingly, the administration of even large doses of tyrosine as either the pure amino acid or the more soluble methyl ester to otherwise untreated animals had no effects on the levels of these metabolites in most instances (McNamee et al. 1980; Scally et al. 1977; Sved and Fernstrom 1981; Sved et al. 1979b). Gibson and Wurtman (1978), however, did find that systemically administered tyrosine resulted in a 15% increase in whole brain MHPG SO<sub>4</sub> levels in rats pretreated with probenecid (to block metabolic egress from the brain). Again, systemic administration of competing TNAAs reduced both tissue tyrosine levels and the rate of catecholamine synthesis.

However, if the experimental animals were given an additional treatment designed to accelerate the firing of dopaminergic or noradrenergic tracts, then the supplemental tyrosine markedly enhanced the accumulation of the catecholamine metabolites (Table 1). For example, when rats were given the dopamine antagonist haloperidol, which accelerates the firing frequency of the nigrostriatal pathway (Bunney et al. 1973) and lowers striatal tyrosine levels (Westerman and Wink 1983), then systemic administration of tyrosine increased catecholamine synthesis; tissue levels of HVA varied directly with those of striatal tyrosine, whereas dopamine levels remained constant (Scally et al. 1977). These initial observations formed the basis for the hypothesis that catecholaminergic neurons become tyrosine sensitive when they are physiologically active, and lose this capacity when quiescent.

The ability of additional tyrosine to enhance catecholamine synthesis in, and release from, only those neurons that are rapidly firing has been shown using a variety of pharmacological as well as physiological treatments. Tyrosine administration increases brain levels of dopamine metabolites when animals are pretreated with reserpine (Sved et al. 1979a), spiperone (Fuller and Snoddy 1982), or anisoleic acid (Fuller and Snoddy 1982), which are thought to increase the firing frequency of nigrostriatal neurons. Also, supplemental tyrosine can enhance ipsilateral dopamine metabolism in rats with unilateral nigrostriatal lesions. Melamed et al. (1980) reported that following a 6-hydroxydopamine-induced nigrostriatal lesion (which destroyed more than 80% of that tract, and thus accelerated the firing of the surviving neurons [Agid et al. 1973]),

tyrosine administration increased dopamine release on the lesioned side (as estimated by the ratios of DOPAC or HVA to dopamine, or to tyrosine hydroxylase activity), but not on the intact side (using the same indices). This effect could be blocked by coadministration of valine (another TNA that effectively competes with tyrosine for transport into the brain) and was not associated with changes in tissue dopamine levels.

Systemically administered tyrosine need not affect the various catecholaminergic pathways in an identical fashion. For example, Sved (1980) found that tyrosine administration normally does not alter the rate of dopamine synthesis (i.e., dopa accumulation after decarboxylase inhibition) in the striatum or in the median eminence. However, following intracerebral injection of ovine prolactin, a treatment that specifically activates tuberoinfundibular neurons projecting to the median eminence (Annunziato 1979; Annunziato and Moore 1978; Moore et al. 1978), tyrosine administration increased the rate of dopamine synthesis in the median eminence, but not in the striatum. Tyrosine supplementation also increases the levels of dopamine metabolites in light-activated retinas *in vivo* but not when the animals are in darkness (Gibson et al. 1983). Retinal dopamine synthesis and turnover can also be altered when rats consume protein or tyrosine-supplemented diets (Gibson 1986, 1988). Low doses of tyrosine also increase dopamine synthesis in brain neurons that exhibit high firing frequencies and bursting activity, such as the mesoprefrontal dopaminergic neurons (Iam and Roth 1984). Interestingly, tyrosine administration can also increase dopamine synthesis (Sved and Fernstrom 1981) in neurons that are not firing frequently, but in which tyrosine hydroxylase has been activated pharmacologically (e.g., in nigrostriatal neurons of rats pretreated with  $\gamma$ -butyrolactone, which inhibits their firing but activates tyrosine hydroxylase by decreasing presynaptic inhibition [Morgenroth et al. 1976; Walters and Roth 1974, 1976; Walters et al. 1972, 1973]).

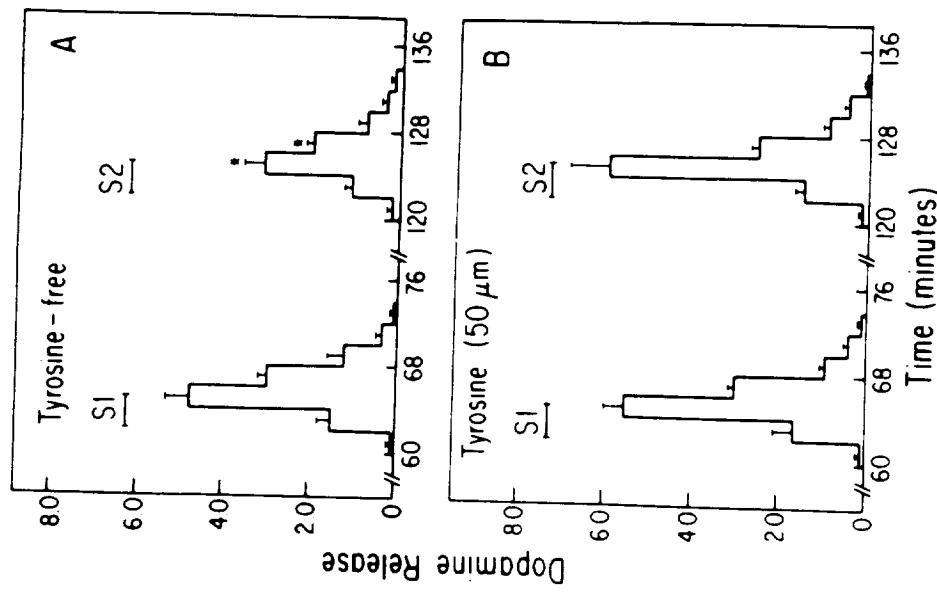
Tyrosine administration can also affect norepinephrine metabolism. For example, the level of the chief metabolic product of norepinephrine, MHPG SO<sub>4</sub>, is elevated in the whole brain when cold-stressed animals are administered tyrosine (Gibson and Wurtman 1978). Also, tyrosine supplementation increases the level of MHPG SO<sub>4</sub> in the brain stem of spontaneously hypertensive rats, but not in normotensive controls or in spontaneously hypertensive rats also given valine (Sved et al. 1979; Yamori et al. 1980). (It is interesting that tyrosine administration apparently fails to affect dopamine metabolism in any brain area of the spontaneously hypertensive rat.) Increases in MHPG SO<sub>4</sub> after tyrosine administration are seen in animals

pretreated with the  $\alpha_2$  antagonist yohimbine (Gibson 1977) or in those animals subjected to tail shock stress (Renstein et al. 1984).

The use of brain levels of catecholamine metabolites as indices of synthesis and release of these metabolites involves assumptions that may or may not be valid (e.g., that the flux of these metabolites out of the brain is unaffected by the experimental treatment). Wisdom requires that before the hypothesis that tyrosine levels affect catecholamine synthesis can be accepted, it should be supported by direct evidence on the release of the transmitter.

#### Studies Using Brain Slices

Much evidence has now been obtained using both *in vitro* brain slice studies and *in vivo* microdialysis studies (see next section). Milner and Wurtman (1985, 1986) examined the effects of adding tyrosine to the superfusate on dopamine release from electrically stimulated rat striatal slices (which were also exposed to the dopamine reuptake blocker nomifensine). Slices were subjected to electrical pulses (20 Hz, 2 milliseconds) of various train lengths (either 600 pulses [30 seconds] or 1,800 pulses [90 seconds]), and the amount of dopamine released into the superfusate medium was correlated with tyrosine concentration. When tissue was superfused in Krebs bicarbonate buffer lacking tyrosine and was subjected to two trains of pulses (1,800 pulses) delivered 60 minutes apart, the amount of dopamine released during the second stimulation period decreased by 20 to 25% (Figure 1-1). However, if tyrosine was included in the medium (50  $\mu\text{M}$ ), then dopamine release remained unaltered after both stimulation periods. Milner and Wurtman (1985) then showed that a tyrosine concentration in the superfusate of at least 20  $\mu\text{M}$  was needed to maintain dopamine release during both stimulation periods in slices stimulated for 30 seconds, while at least 40  $\mu\text{M}$  was needed in tissue stimulated for 90 seconds (Figure 1-2). Tissue that had been stimulated in tyrosine free medium also showed a marked decrease in tyrosine content (up to 50%), as well as in tissue dopamine levels (25%). (The ability of supplemental tyrosine to maintain catecholamine release in the face of repeated firing apparently is not characteristic of all catecholaminergic neurons; norepinephrine release from superfused hypothalamic slices was not sustained by adding tyrosine to the medium [Irie and Wurtman 1987].) Because dopaminergic terminals constitute only a small proportion of the total cellular mass of the striatum, this decrease in tissue tyrosine poststimulation either represented a depletion in noncatecholaminergic cells, as well as dopaminergic cell terminals, or showed that most of the tyrosine in the striatum is located in dopaminergic neurons.

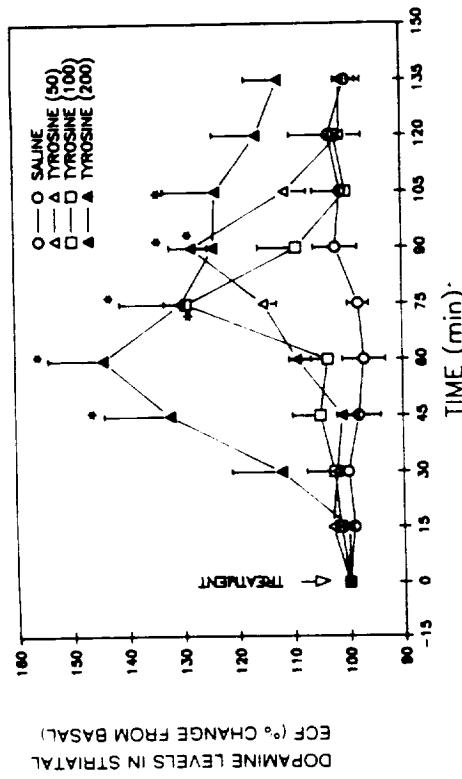


**Figure 1-1.** Release of endogenous dopamine evoked by electrical stimulation from rat striatal slices, expressed as percentage released of final tissue content. (A) Tyrosine free medium; (B) tyrosine-supplemented medium (50  $\mu\text{M}$ ). S1 and S2 were identical trains of 1,800 pulses (60 mA, 2 milliseconds, 20 Hz) delivered 60 minutes apart. Superfusate was collected every 2 minutes and assayed for dopamine by alumina extraction and high-performance liquid chromatography with electrochemical detection. Data were analyzed by paired Student's *t* tests, and values are shown as mean  $\pm$  SEM for four experiments. Asterisk denotes  $P < .05$  when compared to equivalent fractions from S1 (Milner and Wurtman 1986).

Tyrosine, when administered intraperitoneally in doses of 50–200 mg/kg, transiently, but significantly, increased dopamine levels in striatal dialyzates by 28 to 45% above basal values (Aworth et al. 1988) (Figure 1-3). The fact that tyrosine administration can increase dopamine release in otherwise untreated animals suggests that dialysis is able to measure a small pool of newly synthesized, preferentially released dopamine that is too small a proportion of the total dopamine pool to be measured using more conventional neurochemical methods.

methods such as measuring dopamine levels in homogenates (see above). An equivalent dose of tyrosine (200 mg/kg) is more effective at increasing dopamine release in the nucleus accumbens than in the striatum (104% vs. 45%) (During et al. 1988a). This finding agrees with other neurochemical data showing that the nucleus accumbens exhibits a higher dopamine turnover (Beal and Martin 1985) and rate of synthesis (Anden et al. 1983). In each of the previous cases, the effect of supplemental tyrosine on dopamine release was short lived, suggesting that there are feedback mechanisms, perhaps based on autoreceptors or transsynaptic control of firing frequencies, that are activated to restore dopamine release to basal levels. In agreement with this explanation, the duration of tyrosine's (100 mg/kg) effect on dopamine release in the striatum was prolonged and the effect potentiated when animals were pretreated with the dopamine antagonist haloperidol (2 mg/kg) (During et al. 1988b). Also, if surviving nigrostriatal neurons were forced to fire more frequently—for example, after producing partial lesions with 6-hydroxydopamine—then systemically administered tyrosine (100 mg/kg) transiently increased dopamine levels in striatal ECF to 240% of basal values (During et al. 1988b) as compared with 30% in unoperated controls.

Phenylalanine can also affect striatal dopamine release as measured by microdialysis. Its effects vary with dose; a low dose (200 mg/kg) increases dopamine release by 59%; larger doses fail to affect dopamine release (500 mg/kg) or actually inhibit dopamine release by 26% (1,000 mg/kg) (During et al. 1988b) (Figure 1-4). A possible explanation of this triphasic effect of phenylalanine on striatal dopamine release is as follows: rodents have highly efficient hepatic conversion of phenylalanine to tyrosine (Moldawer et al. 1983), so that low doses of phenylalanine preferentially elevate plasma tyrosine levels. Tyrosine is, therefore, more effective at competing for access to the LNAAs carrier (Pardridge 1977) for entry into the brain, where it can act as a substrate for dopamine synthesis. At somewhat higher doses, the hydroxylation of phenylalanine becomes less efficient, so that the plasma tyrosine/phenylalanine ratio approaches unity and neither amino acid has advantage at the LNAAs carrier for transport into the brain. At the highest dose of phenylalanine used, the decrease in dopamine release is likely to reflect at least two processes, for example, the reduction in the plasma tyrosine/LNAAs ratio and the consequent reduction in brain tyrosine levels (Fernstrom and Faller 1978) and the inhibition of tyrosine hydroxylase (Ikeda et al. 1967; Katz et al. 1976).



**Figure 1-3.** Effects of intraperitoneal administration of saline or various doses of tyrosine (50, 100, or 200 mg/kg) on striatal extracellular fluid (ECF) levels of dopamine. Groups of rats ( $n = 5$ ) were anesthetized with  $\alpha$ -chloralose/urethane (0.05/0.5 g per kg ip). Microdialysis probes were placed acutely in the right striatum (A: +0.5; R: 2.5; V: -7) and were perfused with artificial CSF at 1.5  $\mu$ l/minute. After injury release (100–120 minutes post probe implantation) and when basal levels of dopamine in three consecutive collections varied by less than 8%, rats then received either saline or tyrosine (50, 100, or 200 mg/kg, 4 ml/kg) as a suspension in saline. Samples were analyzed every 15 minutes for dopamine by high performance liquid chromatography with electrochemical detection. Groups of five animals were used for each drug treatment. Vertical bars represent standard error of the mean. Statistical significance was measured using unpaired Student's *t* test. Asterisk denotes  $P < .05$ . (Aworth et al. 1988)

relatively few published findings have examined and described effects of tyrosine on catecholaminergic functions.

Systemically administered tyrosine has been shown to ameliorate swim test immobility and to increase open field exploration in mice (Gibson et al. 1982), as well as to increase motor activity in aged mice (Thurmond and Brown 1984). Tyrosine also reverses stress induced inhibition of open field behavior in rats (Lehnert et al. 1984).

The coupling of tyrosine responsiveness to neuronal firing probably explains the paradoxical effects of tyrosine on blood pressure; the amino acid *elevates* blood pressure (and sympathoadrenal catecholamine release) in hypotensive animals (Conhay et al. 1981), but *lowers* blood pressure (without effecting sympathoadrenal catecholamine release) in hypertensive animals (Sved et al. 1979b). This latter effect probably results from tyrosine's conversion to norepinephrine in brain stem neurons active in the depressor pathway; in support of this hypothesis, tyrosine increases brain stem MHPG-SO<sub>4</sub> levels in spontaneously hypertensive rats (Sved et al. 1979b). (Tyrosine fails to affect blood pressure at all in normotensive humans and animals [Glaeser et al. 1979; Sved et al. 1979b].)

Supplemental tyrosine also prevents ventricular arrhythmias in dogs (Scott et al. 1981), reverses renal hypertension in rats (Bresnahan et al. 1980), and restores estrous cycling in aged anestrous female rats (Linnola and Cooper 1976).

Clinically, supplemental tyrosine may be useful for treating some patients with early Parkinson's disease (Gowdon 1979), although its effect apparently is short lived. It may also have some use in depression, given with or without 5-hydroxytryptophan or tryptophan (Gowdon 1979; Mouret et al. 1988; van Pragg and Lemus 1985). Its utility in treating hypertension or other cardiovascular diseases (e.g., cardiac arrhythmias) awaits evaluation. The amino acid may also have some value in prophylaxis or treatment of stress responses; rats subjected to tail shock stress were found, immediately thereafter, to have depressed brain norepinephrine levels, particularly in the locus coeruleus and the hypothalamus, probably reflecting the inability of norepinephrine synthesis to keep up with its release (Lehnert et al. 1984); the animals also showed norepinephrine related behavioral abnormalities and elevated plasma corticosterone levels (Reinstein et al. 1985). All of these changes, including the adrenocortical response, were suppressed by supplemental orally administered tyrosine, but not if the tyrosine was coadministered with another L.NAA (valine) that blocked its brain uptake.

In a preliminary study, Bandaret and Lieberman (1989) investigated the effect of tyrosine on performance, symptoms, and mood

of United States Air Force pilot volunteers under situations of stress (i.e., a cold environment at low barometric pressure). Tyrosine enhanced performance, including reaction time, vigilance, and complex information processing, and reduced subjective symptoms of cold, muscle discomfort, and headache. Mood states (e.g., anxiety and tension) were also improved.

Precursor control of catecholamine release may now be of particular relevance because of the consumption of the artificial dipeptide sweetener, aspartame (56% phenylalanine by weight). If our microdialysis data showing that consumption of phenylalanine can alter dopamine release in rodent brain is also true for humans, then this factor may be involved in the various neurological symptoms sometimes described as being temporally associated with aspartame consumption, for example, seizures (Maher and Pinto 1988) and precipitation of headaches (Johns 1988).

The competitive nature of brain L.NAA uptake may underlie variations in the therapeutic effect of L-dopa, itself an L.NAA. The "on-off" effect in parkinsonian patients receiving L-dopa is significantly worsened by ingestion of a high protein meal (Nutt et al. 1984). A high carbohydrate meal, which elevates the plasma L-dopa ratio by lowering plasma L.NAA levels, exacerbated dyskinesias after L-dopa administration; a high protein meal, which raises plasma L.NAA levels, exacerbated the parkinsonian symptoms (Wurtman et al. 1988).

## CONCLUSIONS

Tyrosine administration increases, sequentially, the "tyrosine ratio" and brain tyrosine levels. With catecholamine neurons, this increase can facilitate synthesis and release of the catecholamine neurotransmitters. In otherwise untreated animals, systemic tyrosine administration causes a transient increase in dopamine release from nigrostriatal neurons. This increase can be enhanced and prolonged by treatments that interfere with multisynaptic or autoreceptor-mediated feedback processes. If animals are subjected to treatments that increase the firing frequency of particular catecholaminergic tracts or nerves, the neurons remain sensitive to changes in the available tyrosine level. The possible use of supplemental tyrosine to treat neurological and behavioral disorders is under examination.

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